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PATENT
ATTORNEY DOCKET NO.: TNX98-03-01
Customer No.: 26839

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Ni, Paul et al.

Serial No.: 10/071,962

Filed: February 8, 2002

For: G-CSF RECEPTOR AGONIST ANTIBODIES AND SCREENING METHODS THEREFOR

Group Art Unit: 1647

Examiner: L. Spector

APPEAL BRIEF

I. Real Party in Interest

The subject application is owned by Tanox, Inc. of Houston, Tx.

II. Related Appeals and Interferences

There are no other appeals or interferences related to the subject application.

III. Status of the Claims

On July 7, 2006, appellant appealed from the final rejection of claims 31-33, 36-38, 40, 45 and 48-50, claims 1-30, 34-35, and 42-43 having been cancelled, and claims 44, 46-47 having been withdrawn from consideration pursuant to a restriction requirement. Claims 39 and 41 are objected to for depending from rejected claims.

Claims 31-33, 36-38, 40, 45 and 48-50 are currently being appealed.

IV. Status of Amendments

The appellant filed an amendment April 10, 2006. In the Advisory Action dated May 2, 2006, the Examiner indicated that the amendment was entered.

V. Summary of Claimed Subject Matter

Appellant's invention relates to agonist antibodies that specifically bind the extracellular domain of the human G-CSF receptor to stimulate cell proliferation and differentiation. The agonist antibodies are capable of dimerizing the receptor or

activating phosphorylation of kinases upon binding. In addition, the agonist antibodies of the present invention stimulate proliferation and differentiation of neutrophils and their progenitor cells. This invention is stated at page 4, lines 21-29, of the specification in the Summary of the Invention. FIG.5A and B show the proliferation of human G-CSF receptor transfected mouse cells stimulated by various mouse monoclonal agonist antibodies, including mAb163-93 and mAb174-74-11, as measured by an MTT assay, illustrating the assay used in identifying agonist antibodies of the present invention.

VI. Grounds for Rejection to be Reviewed on Appeal

A. Claims 31-33, 36-38, 40, 45 and 48-50 have been rejected as anticipated by Cunningham et al. (U.S. Pat. No. 5,506,107).

B. Claims 31-38, 40 and 45 have been rejected as anticipated by Adams et al. (U.S. Pat. No. 6,342,220).

VII. Arguments in Support of Patentability Over the 35 U.S.C. §103(a) Rejection

A. Claims 31-33, 36-38, 40, 45 and 48-50 have been rejected as anticipated by Cunningham et al. (U.S. Pat. No. 5,506,107).

1. The Office's Statements in support of Rejection

In the Final Office Action dated January 9, 2006, the Office asserted that:

> Cunningham et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. At columns 23-24, Cunningham et al. discuss agonist antibodies to the growth hormone receptor, and state that such antibodies may be raised by immunizing animals against growth hormone (and presumably screening the resultant antibodies for agonist properties). Also at columns 23-24, Cunningham et al. disclose such antibodies to be monoclonal, chimeric, or CDR grafted, and compositions comprising such

2. Appellant's Argument that Cunnigham is Non-Enabling Prior Art

Before a reference can even be considered to constitute legally cognizable prior art, it must teach how to make what it discloses. *In re Hoeksema*, 399 F.2d 269, 274, 158 U.S.P.Q. 596, 600-01 (C.C.P.A. 1968) held that the "true test of any prior art relied

on to show or suggest that a chemical compound is old, is whether the prior art is such as to place the disclosed 'compound' in the *possession of the public*" (emphasis added).

Cunnigham does not disclose any agonist antibodies to G-CSF-R. In the parent application U.S. Appl. No. 09/303,155, in an Office Action dated January 9, 2001, the present Examiner admitted that the Cunnigham reference did not disclose any anti-GCSF agonist antibodies. The mere disclosure of the desire to make an agonist antibody to G-CSF is not enabling, and no one prior to the present inventors had made such an antibody. No reference was cited by the Examiner disclosing actual agonist antibodies to G-CSF.

Appellants noted in the argument presented in the Response filed June 29, 2005, that it is easy to obtain a neutralizing antibody because one merely blocks binding of the ligand, i.e. the G-CSF protein, to the receptor. However, an agonist antibody is much more difficult to obtain because it must bind to the receptor in a proper confirmation, dimerizing the two (or more) subunits of the receptor and triggering the activation of the receptor in the same manner as the native ligand. In the paper submitted by Appellants by Schneider et al. Blood 59(2):473-480 (1997) (See Exhibit IX), the authors highlight the difficulty in making dimerizing agonist antibodies and pose the question "Why are agonist antibodies to EPO-R so rare?". In that paper, they stated all of their monoclonal antibodies specific for the extracellular domain of EPO receptor should have dimerized the receptor, but in fact only one in the 48 isolated antibodies did so. They also point out that EPO-R is part of a cytokine receptor superfamily, which includes receptors for IL-2, growth hormone, G-CSF, GM-CSF, as well as others. Appellants argued that given the difficulty of making EPO-R agonist antibodies and the similarity between EPO-R and G-CSF-R, a similar situation is true for G-CSF, that agonist antibodies that dimerize and activate the G-CSF-R would be difficult to make and more difficult to identify.

Indeed this proved to be the case in the present invention. In a declaration made by the First Inventor Baufo Ni, in the parent application 09/303,155, stated:

> "[M]y coworkers and I screened approximately 500,000 candidates in order to obtain 10 potential agonist antibodies. This required high-throughput screening, with a success ratio of only 1 in 50,000. Measuring ^{3}H-thymidine incorporation at this level would not have

been practical from either a cost standpoint or from the risk of radioactive contamination. We also found that using the D4 cell line expressing an artificial G-CSF receptor, similar in nature to that used by Cunningham, was not sufficiently predictive of a true agonist. As seen in Figure 5B of our application, MAb174-12 (solid triangles) appears to be an agonist antibody based on the amount of uptake of MTT as compared to the native G-CSF (solid squares). However, when this same antibody was tested in a colony-formation assay using human bone marrow cells (an assay that more closely mimics a true environment of cells with native human G-CSF receptor) it showed no agonist activity. This clearly shows that there is a substantial difference between an artificial cell-line expressing a recombinant receptor and cells with an endogenous receptor.

Moreover, receptor orientation and disposition has been found to be important to receptor function. Receptor function that is as close to the endogenous form is essential in identifying a true receptor agonist. Because our artificial cell line having a recombinantly expressed G-CSF receptor was not sufficiently predictive of true agonist activity, it is highly unlikely that the hybrid receptor used by Cunnigham having an extracellular domain of one receptor type fused to the intracellular domain of another receptor type could sufficiently mimic true receptor function in order to isolate a functional agonist for G-CSF receptor.

Other researchers in the field support the conclusion that an artificial cell-based assay system measuring ^{3}H-thymidine incorporation is too unpredictable to be used to identify agonists for a cytokine receptor in this family. I draw the Examiner's attention to the reference Schneider et al. (Exhibit B). These authors observed that MoAb34 appeared to be agonistic in an assay measuring ^{3}H-thymidine incorporation using artificial cell lines (figure 3B), but in the colony formation assay using human CD34^{+} cells reported in Table 2, this MoAb showed essentially no agonist activity.

Appellants submitted that the assay taught by Cunningham would not lead one to isolate a valid agonist antibody, hence failing to teach "how to make" and thus would not have resulted in putting the public in possession of the invention by merely disclosing the desire to make such an antibody.

Thus, due to the rarity of agonist antibodies to EPO-R which is a member of the same family of receptors as G-CSF, the lack of an adequate assay for detecting agonist antibodies to G-CSF-R, and the lack of any evidence that an agonist antibody to G-CSF-R was made prior to the present invention, makes the Cunnigham reference inadequate prior art, lacking enablement. Moreover, as evidenced by the declaration of the Inventor B. Ni, identifying agonist antibodies to G-CSF-R was even more infrequent that EPO-R (i.e., 1:50,000 vs. 1:48). Thus, the public was not in possession of a G-CSF-R agonist antibody prior to the filing of the present application and therefore, the

Cunnigham reference cannot and does not anticipate the currently claimed invention.

In view of the fact that Cunnigham is not valid prior art, the Examiner made a clear error in rejecting the claims as anticipated, and Appellants request that the rejection be reversed.

3. **Appellant's Argument that Cunnigham does not anticipate Claim 49**

Claim 49 is directed to the specific CDR sequences of agonist antibodies mAb166-93 and mAb174-24-11 and their functional variants. The Examiner offered no sequence comparison and indeed there are no sequences disclosed in the Cunnigham reference. Therefore, the rejection of claim 49 as anticipated by a reference with no sequences is clearly erroneous and should be reversed.

B. Claims 31-38, 40 and 45 have been rejected as anticipated by Adams et al. (U.S. Pat. No. 6,342,220).

1. **The Office's Statements in support of Rejection**

In the Final Office Action dated January 9, 2006, the Office asserted that:

Adams et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. Fragment and single chain antibodies are discussed at column 18. Methods of making the antibodies are disclosed at column 25. Thus, Adams discloses the desirability of obtaining agonists of the G-CSF receptor, and further discloses methods of obtaining agonist antibodies consistent with the claims. Accordingly, Adams et al. fairly place the claimed invention in the hands of the public.

2. **Appellant's Argument that Adams does not anticipate is Non-Enabling Prior Art**

Adams et al. does not disclose making or any examples of G-CSF agonist

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antibodies. The only disclosure at column 12 is a definition of cytokines and a list of examples. There is no disclosure of making agonist antibodies to G-CSF. Column 12, line 56 states:

> "Cytokine superfamily receptors" and "hematopoietic growth factor superfamily receptors" are used interchangeably herein and are a group of closely related glycoprotein cell surface receptors that share considerable homology including frequently a WSXWS domain and are generally classified as members of the cytokine receptor superfamily (see e.g. Nicola et al., *Cell*, 67:1–4 (1991) and Skoda, R. C. et al. *EMBO J.* 12:2645–2653 (1993)) Generally, these receptors are interleukins (IL) or colony-stimulating factors (CSF). Members of the superfamily include, but are not limited to, receptors for: IL-2 (b and g chains) (Hatakeyama et al., *Science*, 244:551–556 (1989); Takeshita et al., *Science*, 257:379–382 (1991)), IL-3 (Itoh et al., Science, 247:324–328 (1990); Gorman et al., *Proc. Natl. Acad. Sci.*

The list continuing on to the next col. 13, at line 13, does disclose G-CSF-R as a member of this family, but this definition does not state "agonist antibodies to" members of this family. The only other reference that the undersigned found was at column 24, line 53, and column 38, line 22, referring to the treatment of a mammal with an antibody in combination with a cytokine, e.g., G-CSF, but no reference to making agonist antibodies to the receptor G-CSF-R. This reference only discloses the making of agonist antibodies to thrombopoetin (c-mpl). Therefore, this reference does not anticipate the claimed invention.

3. Appellant's Argument that Adams is Non-Enabling Prior Art

Even if one interpreted the disclosure at column 12 as disclosing a desire to make agonist antibodies to G-CSF-R, the Adams reference fails to teach "how to make" agonist antibodies to G-CSF-R, and thus would not have resulted in putting the public in

possession of the invention by merely disclosing the agonist antibodies to thrombopoetin (c-mpl). For all of the reasons stated in Section A above, Adams is not valid prior art and does not put the public in possession of the claimed invention.

In view of the fact that Adams does not anticipate the claimed invention for failing to disclose agonist antibodies to G-CSF, and Adams is not valid prior art, the Examiner made a clear error in rejecting the claims as anticipated, and Appellants request that the rejection be reversed.

C. Summary

For the foregoing reasons, Appellant believes that the Office's rejection of claims Claims 31-33, 36-38, 40, 45 and 48-50 were erroneous, and reversal of these rejections is respectfully requested.

Respectfully Submitted

By: Cheryl A Liljestrand

Cheryl A. Liljestrand
Reg. No. 45,275

Dated: October 10, 2006.